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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/577,285	10/10/2006	Barbara Podobnik	33138-US-PCT	2838

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CORPORATE INTELLECTUAL PROPERTY
ONE HEALTH PLAZA 104/3
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EXAMINER	
STOICA, ELLY GERALD	

ART UNIT	PAPER NUMBER
1647	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/577,285	PODOBNIK ET AL.	
	Examiner	Art Unit	
	Elly-Gerald Stoica	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-15* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-15* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of the claims

1. Claims 1-15 are pending and are examined.

Claim Rejections - 35 USC § 102

2. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

3. Claims 1, 3, 4 5, 6, 7, 12, 13 rejected under 35 U.S.C. 102(b) as being anticipated by Goldenberg et al. (U. S. Pat. No: 6,432,449).

The claims are drawn to a stable pharmaceutical composition of granulocyte-colony stimulating factor (G-CSF), wherein the composition has a pH value in the range from 4.2 to 4.8 and comprises: a therapeutically effective amount of G-CSF, and an acid, wherein the composition is free of a surfactant. The composition also comprises a polyol and/or a pH buffering system and/or one or more pharmaceutically acceptable excipient(s). The G-CSF is non-glycosylated and the composition is aqueous. The acid in the composition is selected from the group consisting of acetic acid and HCl and the

polyol is selected from the group consisting of sorbitol, glycerol, inositol and mannitol. The pH buffering system is acetic acid/acetate.

Goldenberg et al. teach a preparation of a protein drug (G-CSF)-containing alginate ethyl ester (DE=30 mol %) gel and the in vitro sustained release from this gel (Example 5).

The G-CSF used is from AMGEN (www.amgen.com/about/milestones.html) which made the G-CSF in E. Coli bacteria and therefore the compound is non-glycosylated. To a solution of 2.39% ethyl ester alginate (30 mol %, 0.5 ml) is added 0.1M acetate buffer (pH 4.5, 100 µl), G-CSF (104 µl, 48.2 mg/ml, HCl pH3) and distilled water (246 µl). The mixture is stirred well. A suspension of 1M $CaHPO_4$ (10 µl) and a solution of 1.68M δ-gluconolactone (40 µl) are thoroughly stirred into this mixture. The final mixture (0.2 ml) is cast on the inside of a tube and left overnight at 4°C to gel. After overnight storage of the gel in vitro release is conducted in 10 mM Tris buffer, pH 7.5. This cast ethyl ester alginate gel with 30 mol % degree of esterification exhibits less than 5% burst and sustained release showing 20% released in 1 day and 40% released in 2 days (Example 5).

The elements of the claimed invention from the instant application are anticipated by Goldenberg et al., since the pH is 4.5, the G-CSF is present, by presentation, no surfactants are added and an acid (HCl) is present. Moreover, the ethyl ester alginate is only one third esterified and according to the definition of the polyol in the instant specification, is a polyol. The buffering system is acetic acid/acetate, the composition is aqueous and the δ-gluconolactone is a known pharmaceutical excipient. Goldenberg et

al. also mention the possibility of using glycerol in the compositions (col. 4, line 15). The stability of the composition is underscored by the fact that even under conditions conducive to extraction of the G-CSF from the composition, only 40% was released after 2 days. Thus, claims 1, 3, 4, 5, 6, 7, 12, 13 are anticipated by Goldenberg et al.

4. Claims 1-3, 5-9 and 12-15 are rejected under 35 U.S.C. 102(e) as being anticipated by Liu et al. (U. S. Pat. No.: 6,875,432).

Liu et al. teach a stable formulation of reduced viscosity comprising a protein having a pH lower (~4.0 to ~ 5.3). The pH is altered through the addition of a pharmaceutically acceptable acid, base or buffer, and is added in an amount of at least about 10 mM; the acid, base and/or buffers are monovalent and are selected from the group consisting of acetic acid or hydrochloric acid. The pH is any tenth pH value within those enumerated above; example values are pH 4.0, 4.1, 4.2, 4.3, 4.4, 4.5, 4.6, 4.7, 4.8, 4.9, 5.0, 5.1, 5.2 and 5.3. In another particular aspect, the formulation **may** (but just as an option, hence other embodiments are surfactant free) further comprise a surfactant such as polysorbate (col. 3, lines 17-43). The invention also contemplates a reconstituted formulation that further comprises a lyoprotectant such as a polyol such as trihydric or higher molecular weight sugar alcohols, e.g. glycerin, dextran, erythritol, glycerol, arabitol, xylitol, sorbitol, and mannitol. One of the proteins encompassed by the invention is G-CSF (col. 6, line 41). The formulations of the invention are administered to a mammal in need of treatment with the protein, preferably a human, in accord with known methods, such as intravenous administration as a bolus or by continuous infusion over a period of time (col. 27, lines 18-23). Inherently this means a liquid

formulation and, since the components of the formulation are all water soluble, it will necessarily be aqueous.

Thus, claims 1-3, 5-9, and 12-15 are anticipated by Liu et al.

Claim Rejections - 35 USC § 103

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

7. Claims 4, 10 and 11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Liu et al. (U. S. Pat. No.: 6,875,432) in view of Platz et al. (U. S. Pat. No.: 5, 284,656) and in further view of Sumida et al. (U. S. Pat. No.: 6,776,983).

The claims are drawn to a stable pharmaceutical composition of granulocyte-colony stimulating factor (G-CSF), wherein the composition has a pH value in the range from 4.2 to 4.8 and comprises: a therapeutically effective amount of G-CSF, and an acid, wherein the composition is free of a surfactant. The composition also comprises a

polyol and/or a pH buffering system and/or one or more pharmaceutically acceptable excipient(s). The polyol is sorbitol, present in an amount of 1%-10% or 3%-8%.

The teachings of Liu et al. were presented supra. Liu et al. does not offer a range for the sorbitol in the composition taught in their invention and does not specify the source of the G-CSF used. Platz et al. teach G-CSF formulations that will typically comprise G-CSF dissolved in water and include a buffer and a simple sugar (e.g., for protein stabilization and regulation of osmotic pressure). Examples of buffers which may be used are sodium acetate, citrate and glycine. Examples of sugars which can be utilized are mannitol and sorbitol, usually in amounts ranging from 1% to 10% by weight of the formulation (col. 3, lines 48-61). Sumida et al. teach stable granulocyte colony-stimulating factor-containing formulations comprising a G-CSF and having a pH of 7 or less (abstract). G-CSF may be prepared by any process, e.g., they may be extracted and purified by various techniques from cultures of a human tumor cell line or may be produced by genetic engineering in cells of E. coli (col. 2, lines 16-30). G-CSF produced in E. coli is non-glycosylated.

It would have been obvious for a person of ordinary skill in the art at the time that the invention was made to try the finite number of sorbitol concentration ranges of Platz et al. for the composition of Liu et al., including the non-glycosylated G-SCF of Sumida et al., in a attempt to provide an optimal formulation for the G-CSF composition, since persons of ordinary skill in the art have good reason to pursue the known options within their technical grasp. A person of ordinary skill in the art would have had an excellent expectation of success given the teaching of Liu et al., Platz et al and Sumida et al.

Double Patenting

8. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

9. Claims 1-5 and 8-11 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-10 of copending Application No. 10583157. Although the conflicting claims are not identical, they are not patentably distinct from each other because the G-CSF composition that is claimed in the Application No. 10583157 can be construed as to be the G-CSF composition that has the limitations claimed by the instant Application.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

10. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Elly-Gerald Stoica whose telephone number is (571) 272-9941. The examiner can normally be reached on 8:30-17:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary B. Nickol can be reached on (571) 272-0835. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

LORRAINE SPECTOR
PRIMARY EXAMINER